Feature: Sights on a Cure

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Stem cell scientists have macular degeneration in the crosshairs

by Emmanuel Romero

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At a 2008 Annual Exhibition in San Francisco's City Hall, abstract painter Virginia Knepper Doyle unveiled "Family Stories 2". The canvas's deliberate swirls of green, blue, beige and olive acrylic paint are meant to signify unity and kinship.

This year, Doyle is following up her "Family" series with a new series centered on Asian bamboo forests. As a nature enthusiast, she believes humankind can rescue these beautiful forests from the brink of extinction. This creativity and passion have taken Doyle's art to audiences around the world, to galleries from New York to Paris.

What her admirers may not know is that Doyle has been visually impaired for the last 11 years, after macular degeneration robbed her of much of her central vision. Since her diagnosis, Doyle has left Impressionism in favor of abstract art and has seen her critical acclaim grow.

"I was trying to be somebody else," she said. "The real me came out, and I didn't care if I made mistakes."

This professional success comes at a price; Doyle has difficulty reading and recognizing faces. Because she cannot drive anymore, her husband has to take her to all her appointments.

Doyle misses her lost independence and is looking to stem cell scientists for hope. With good cause. Many experts consider macular degeneration to be a disease where stem cells could provide relief sooner rather than later (See Window to Therapy below). The path from current animal studies to human therapies does still have obstacles, including an overzealous immune system, temperamental stem cells and the pesky problem of how to get those cells into the eye. Yet, several research groups, including some in California, think they may be testing stem cell based therapies in patients within the next few years.

A Hole in the Vision

Macular degeneration is a leading cause of vision loss in senior citizens. According to the National Eye Institute, more than 1.7 million Americans have the disease, in which cells in the back of the eye slowly die.

These cells, called retinal pigmented epithelia, or RPE cells, form a nourishing blanket over the light-collecting cells of the retina. In the early, or "dry," stage of the disease, the RPE cells at the center of a person's vision, called the macula, atrophy. As their nourishing layer disappears, the light-collecting cells wither as well, leaving a noticeable distortion in the visual world. Sometimes the disease progresses into the second and more severe stage, known as "wet" macular degeneration, in which abnormal blood vessels begin to grow through the macula. These vessels can leak and lead to scarring and eventual vision loss.

Nobody knows why RPE cells start dying off, but smoking, a high cholesterol diet and sun exposure all seem to play a role. These risk factors have a common denominator – age, said Gabriel H. Travis, professor of ophthalmology and biological chemistry at the University of California, Los Angeles, School of Medicine. Furthermore, some patients share a family gene that predisposes them to the disease.

A growing population portends more future senior citizens. By the year 2020, more than 450,000 Californians will be struck by age-related macular degeneration, according to Mark Humayun, professor of ophthalmology and biomedical engineering at the University of Southern California. Given the high cost of treating blindness and the possible lost income to patients and their caregivers, finding a therapy for the disease could provide a significant benefit to the economy.

Permanent Solutions

Patients with macular degeneration have few options. Currently, no treatment for dry macular degeneration exists, though past research suggests patients may slow the disease's progression by taking antioxidants such as lutein and zeaxanthin. Abnormal blood vessel growth of wet macular degeneration can be arrested with regular injections of expensive drugs that block new blood vessel growth directly into the eye.

"Sometimes, with other patients, the injections work and people see perfectly again, but with me, that's not going to happen," Doyle said of her monthly Lucentis treatment. "The best I can hope for is to not get worse."

Researchers have struggled to find a more permanent solution, including two surgical procedures. While one surgery transplants healthy RPE cells from one part of the retina to the macula, another surgery cuts the macula out altogether and relocates it on top of healthier cells. Either way, there are not enough RPE cells to work with in a patient's eye. And there are risks.

"Because you cut the retina, 20 to 30 percent of the time, the retina completely detaches," Humayun said at a talk to CIRM's Governing Board in April. "You're left with poorer vision than you started." Humayun now has a Disease Team Research Award to move his work to human clinical trials.

Building a Better Blanket

Scientists like Humayun, Travis and Martin Friedlander of the Scripps Research Institute believe they can coax stem cells to form a blanket of RPE cells for transplantation. This idea is built on past experiments using RPE cells from cadavers for transplantation. The procedure showed initial promise, but hopes evaporated once patients' immune systems rejected the foreign tissue.

In the past, many scientists thought of the eye as being largely sheltered from immune activity. However, when a disease such as macular degeneration eats away at the barrier between the circulatory system and retinal tissue, immune reactions are more likely, said Friedlander, professor of cell biology.

In order to avoid immune-rejection, Friedlander has an Early Translational grant to create RPE cells by reprogramming a patient's own skin cells into induced pluripotent stem (iPS) cells, which possess a versatility similar to embryonic stem cells and thus should have the capacity to form RPE cells. If transplant cells come directly from the patient, immune rejection is less of a worry. As techniques to create iPS cells rapidly evolve, Friedlander vows to stay at the forefront to develop the safest, most efficient methods of reprogramming.

Thus far, Friedlander's team has turned iPS cells into what look like RPE cells that produce the same proteins as their natural counterparts. However, they have not yet tested whether the cells actually work. The team must also make sure the RPE cells they use are pure and do not include the original, immature cells, which can form tumors. Friedlander's team hopes to prove that his cells work and are safe in animals, then move on to human clinical trial, within the next few years.

Like Friedlander, Travis has an Early Translational grant to develop stem cell based therapies for macular degeneration. He also believes he can coax iPS cells derived from the skin to form RPE cells for transplantation. However, Travis' team has a second goal of tapping into the eye's own stem cells. Because Travis can harvest these cells from patients themselves, they pose less risk for immune-rejection, just like iPS cells. Both sources present different advantages. While iPS cells are more accessible, the eye's stem cells may be easier to coax into retinal cells and are less likely to form tumors.

If things go well, Travis's team hopes one of these cell supplies will reach clinical trial in the next few years.

Location, Location, Location

Even if researchers like Travis, Friedlander and Humayun, who is carrying out similar work creating RPE cells from embryonic stem cells, are successful, the issue remains of how to deliver the new cells to the right place. This may involve injections directly under the retina, or implanting cells grown on a thin sheet. One collaborator on Travis' team has already injected RPE cells in rodents, while Humayun succeeded with implanting RPE grown on biodegradable sheets in rabbit models.

Similar techniques, pioneered at University College London, show evidence that this procedure may work. Ophthalmology professor Peter Coffey, who is part of Humayun's disease team, made RPE cells from human embryonic stem cells. He placed the RPE cells on a disk as thin as cling film, and implanted the disk into a pig's retina during a procedure that took 40 minutes. These transplanted RPE cells properly nourished the light-collecting cells of the retina. Coffey and his research group hope to treat patients within a few years.

Busy with her successful art career, Doyle may not have the time to follow the day-to-day successes and setbacks of stem cell-based therapies. But that doesn't mean she's not eager for a cure.

"I can't wait," she said. "I just wish [stem cell research will succeed] with all diseases."

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